

CLAIMS

1. A method for analyzing at least one reaction medium comprising at least one cell C, said method 5 being characterized in that:

(i) the cell C is deposited onto a support S comprising a substantially planar surface, in the form of an aqueous drop on said surface;

10 (iv) the reaction medium is prepared and introduced into the mass spectrometer;

(v) the reaction medium is desorbed and ionized;

(vi) the mass spectrum of the reaction medium is recorded and analyzed.

15 2. The method as claimed in claim 1, characterized in that, in a second step (ii), the substantially planar surface of the support S onto which the aqueous drop containing the cell C has been deposited is covered with a separating film F that allows gases to pass 20 through and prevents evaporation of the aqueous drops deposited onto the support S.

25 3. The method as claimed in claim 1 or claim 2, characterized in that, in a third step (iii), the cell C is subjected to a stimulation.

4. The method as claimed in claim 3, characterized in that the stimulation to which the cell C is subjected is chosen from:

30 - the introduction of a reagent R,
- being brought into contact with one or more cells,
- a supply of energy,
- the application of an electric field or of a magnetic field,
35 - an optical treatment.

5. The method as claimed in any one of claims 1 to 4, characterized in that the attachment of the drops to the support S occurs due to surface tension forces.

6. The method as claimed in any one of claims 1 to 5, characterized in that the depositing of the aqueous drops containing a cell or a reagent onto the support S, and optionally under the separating film, is carried out by means of fine capillaries.

7. The method as claimed in any one of claims 1 to 5, characterized in that the depositing of the aqueous drops containing a cell or a reagent onto the support S is carried out by means of a piezoelectric system.

8. The method as claimed in any one of claims 4 to 7, characterized in that the reagent R is chosen from: inorganic molecules, natural organic molecules, molecules derived from organic synthesis or from combinatorial synthesis, molecules extracted from biological samples, and molecules extracted from biological samples, that have been modified by synthesis, in particular single-stranded and double-stranded DNAs, single-stranded and double-stranded RNAs, proteins and peptides.

9. The method as claimed in any one of claims 1 to 8, characterized in that it comprises one or more steps consisting in treating the reaction medium directly on the support S before it is introduced into the mass spectrometer.

10. The method as claimed in claim 9, characterized in that it comprises at least one treatment step chosen from: cell lysis, one or more washes, the adsorption or the attachment of molecules.

11. The method as claimed in any one of claims 1 to 10, characterized in that it comprises at least one step consisting in treating the reaction medium or media placed on the support S with a solution of molecules that promote desorption.

12. The method as claimed in any one of claims 1 to 11, characterized in that the preparation with a view to introduction into the mass spectrometer comprises at 5 least one step selected from: freezing the reaction medium; drying with or without heat treatment and with or without a vacuum; fixing by means of a treatment with an agent such as methanol or formaldehyde.

10 13. The method as claimed in any one of claims 1 to 12, characterized in that the preparation with a view to introduction into the mass spectrometer comprises the addition to the reaction medium of one or more acid molecules that are small in size and absorb light, 15 followed by drying.

14. The method as claimed in any one of claims 1 to 13, characterized in that it comprises at least the following steps:

20 - introduction of the reaction medium or media placed on the support S into a mass spectrometer tube;
- application of a vacuum and of an electric field in the spectrometer tube;
- application of a desorption/ionization treatment 25 in a controlled and sequenced manner on the sample(s);
- detection of the mass of the ions formed.

15. The method as claimed in any one of claims 1 to 14, characterized in that it comprises at least one 30 step consisting in comparing the data recorded with a mass spectrum bank.

16. A device for analyzing at least one reaction medium comprising at least one cell C, this device 35 being characterized in that it comprises:

- a support S comprising a substantially planar surface,
- means for depositing onto said surface aqueous drops containing the cell C,

- means for desorbing and ionizing the reaction medium,
- a mass spectrometer.

5 17. The device as claimed in claim 16, characterized in that it also comprises a controlled-atmosphere chamber in which the support S is placed so as to allow the survival of the cell C.

10 18. The device as claimed in claim 17, characterized in that the controlled-atmosphere chamber is an incubator at a temperature ranging from 35 to 42°C, preferably between 36.5 and 37.5°C, the CO₂ level is preferably maintained at between 3 and 5%, and the 15 oxygen O₂ level is preferably that of ambient air.

19. The device as claimed in any one of claims 16 to 18, characterized in that the surface of the support S is covered with a separating film F that allows gases 20 to pass through and prevents evaporation of the aqueous drops deposited onto the support S.

20. The device as claimed in claim 19, characterized in that the film F is chosen from:

25 - a non-water-miscible liquid;
- a gas;
- a flexible, solid film;
- a rigid honeycombed cover made of porous material, the size of the cavities being adjusted so as to be 30 able to contain the drop of cell(s) and, optionally, a drop of reagent.

21. The device as claimed in any one of claims 16 to 20, characterized in that the support S consists of a 35 plate that is made of silicon, of glass or of a polymer.

22. The device as claimed in any one of claims 16 to 21, characterized in that the support comprises an electrically conducting layer.

5 23. The device as claimed in any one of claims 16 to 22, characterized in that the support S has a substantially planar surface comprising at least one means for receiving the aqueous drops.

10 24. The device as claimed in claim 23, characterized in that the means for receiving the aqueous drops consists of one of the following means:

- the support S exhibits a hydrophobic nature on its planar surface and comprises one or more hydrophilic areas;
- the support S comprises cavities of a depth ranging from 1 micron to 1 millimeter on its planar surface;
- the support S is a plate equipped with outgrowth of small thickness, from 1 micron to 1 millimeter, arranged on its surface and intended to promote the attachment of the drops;
- the support S is a plate equipped with at least one wire, onto which the drops attach.

25. The device as claimed in any one of claims 16 to 24, characterized in that the support S of the device is mobile.

30 26. The device as claimed in any one of claims 16 to 25, characterized in that the aqueous drops containing one or more cells comprise a culture medium.

35 27. The device as claimed in any one of claims 16 to 26, characterized in that the means are connected to a control device that allows it to be automated.

28. The device as claimed in any one of claims 16 to 27, characterized in that the support S comprises means for receiving the drops, arranged regularly in the form of a matrix.

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29. The device as claimed in any one of claims 16 to 28, characterized in that it comprises at least one piece of equipment for measuring the mass of a sample by means of mass spectrometry, said piece of equipment comprising a spectrometer tube, a device for creating a vacuum in said tube, electrical means for applying an electrical acceleration potential in the tube so as to accelerate the molecules of the sample to be analyzed, a means for detecting the mass of the ions formed, a means of introducing the support S into the tube, and a means for the desorption and the ionization of the sample to be treated.

30. The device as claimed in any one of claims 16 to 29, characterized in that the desorption means is selected from: a laser beam, a beam of ions, a beam of neutral atoms, a beam of electrons, and the spraying of a liquid sample.

25 31. The device as claimed in any one of claims 16 to 30, characterized in that the desorption/ionization means is selected from:

- MALDI: matrix assisted laser desorption ionization
- 30 ○ SELDI: surface enhanced laser desorption ionization
- SIMS: secondary ion mass spectrometry
- SNMS: secondary neutral mass spectrometry
- ESI: electrospray ionization
- 35 ○ FAB: fast atom bombardment
- APCI: atmospheric pressure chemical ionization.

32. The device as claimed in any one of claims 16 to 31, characterized in that the means of measuring the mass is selected from:

- 5 TOF: time of flight,
- MS/MS: tandem mass spectrometry or multidimensional mass spectrometry,
- quadrupole (or ion trap),
- FT-MS or FT-ICR: Fourier-Transform mass spectrometry - ion cyclotron resonance.

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33. The use of a device as claimed in any one of claims 16 to 32, for identifying modifications that have been involved in a cell culture subsequent to a stimulation.

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34. The use of a device as claimed in any one of claims 16 to 32, for studying the change over time of the response of a cell or of a set of cells to a stimulation.